TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSEs) (including Creutzfeldt-Jakob disease)

✓DISEASE AND EPIDEMIOLOGY

Clinical Description:

Transmissible spongiform encephalopathies are a group of rare, rapidly progressive, and fatal neurologic diseases characterized by the absence of inflammation, loss of brain tissue in a spongiform pattern, and an unusually long incubation period.

Creutzfeldt-Jakob disease (CJD) is by far the most common TSE. Its symptoms include confusion progressing to dementia, as well as early personality changes and movement disorders including ataxia (lack of muscle coordination) and dysarthria (difficulty in speech). Myoclonus (muscle twitching) and other neurologic symptoms appear late. Fever is not characteristic. The majority (85-90%) of CJD cases are sporadic, however variant CJD (vCJD), iatrogenic CJD (iCJD), and familial CJD (fCJD) have also been documented. fCJD is the second most common form of the disease, accounting for approximately 10-15% of cases worldwide. iCJD occurs in <5% of cases. vCJD is distinguished from sCJD by a typical younger age of onset, early psychiatric and behavioral symptoms (depression or psychosis), painful sensory symptoms (e.g., “stickiness” of the skin), delayed onset of unsteadiness, difficulty walking and involuntary movements.

Clinical and Pathologic Characteristics Distinguishing Classic CJD from Variant CJD

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/ behavioral symptoms; painful dyesthesiasis; delayed neurologic signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
"Pulvinar sign" on MRI	Not reported	Present in >75% of cases
Presence of "florid plaques" on neuropathology	Rare or absent	Present in large numbers
Immunohistochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected

Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein	Not reported	Marked accumulation of protease-resistance prion protein

Table courtesy CDC

Gerstmann-Sträussler-Scheinker Syndrome (GSS) characterized by the loss of coordination, often followed by dementia. It is a hereditary TSE caused by a mutation in the prion protein.

Kuru is an acquired prion disease that is now virtually extinct. It was first described in members of a native tribe in New Guinea known to practice cannibalism. Its symptoms are similar to GSS.

Fatal Insomnia is a disease characterized by trouble sleeping, followed by insomnia and dementia. It can be sporadic (sFI) or familial (FFI).

Causative Agent:

TSEs are also called prion diseases and are thought to be abnormal proteins (protease-resistant prion protein, or PrP-res) that can trigger chain reactions causing normal proteins in the brain to change to the abnormal protein. These abnormal proteins are resistant to enzymatic breakdown, and they accumulate in the brain, leading to damage. In addition to the four human prion diseases, there are five animal prion diseases. These diseases include scrapie in sheep and goats, chronic wasting disease (CWD) in deer and elk, transmissible mink encephalopathy (TME), feline spongiform encephalopathy, and bovine spongiform encephalopathy (BSE) in cows (also called "mad cow disease").

Human TSE	First Reported
Creutzfeldt-Jakob Disease (CJD):	
Sporadic (sCJD)	**1921**
Familial (fCJD)	**1924**
Iatrogenic (iCJD)	**1974**
Variant (vCJD)	**1996**
Gerstmann-Sträussler-Scheinker Syndrome (GSS)	**1936**
Kuru	**1957**
Fatal Insomnia:	
Familial (FFI)	**1986**
Sporadic (sFI)	**1999**

Table courtesy WHO

Differential Diagnosis:

TSEs should be considered in the differential diagnosis of persons presenting with progressive dementing disorders. There are many different conditions that cause progressive dementing disorders, the most common being Alzheimer's disease. Other causes include, but are not limited to, vascular dementia, Lewy body disease, cerebellar degeneration, frontotemporal dementia (e.g. Pick disease type and motor neuron disease type), progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, metabolic encephalopathies, drug-induced encephalopathies (e.g. bismuth,

amitriptyline, mianserin, lithium, baclofen), viral encephalitis, multiple cerebral abscesses, and AIDS-dementia.

Laboratory identification:

Routine laboratory and diagnostic tests are rarely helpful in establishing a diagnosis of CJD or any other TSE. However, these tests may be useful in the differential diagnosis. The National Prion Disease Pathology Surveillance Center (NPDPSC) at the Division of Neuropathology at Case Western Reserve University is the leading institution in the US for diagnosing TSEs. It is supported by CDC, and all of their services are performed free of charge. If a case of CJD or any other TSE is suspected, testing should be coordinated through NPDPSC.

14-3-3 protein assay

Elevated levels of the 14-3-3 protein in CSF have been reported as helpful in diagnosis. 95% of patients with definite sCJD and 93% of patients with probable sCJD have been reported to have elevated levels of the protein. However, elevations in the protein also occur with other diseases, and a positive test should be considered in conjunction with clinical history.

Immunohistochemistry

This test is run by NPDPSC on fixed brain tissue. It tests for whether the specimen i**s** positive or negative for prion disease based on immunostaining of the prion protein. When possible, it can also establish a tentative diagnosis regarding the type of prion disease.

Western Blot

This test is run by NPDPSC on frozen brain tissue**.** It tests for whether the specimen is positive or negative for prion disease based on Western blot analysis of the tissue. When possible, it can also establish a tentative diagnosis regarding the type of prion disease.

PrP Gene Sequencing

This test is run by NPDPSC on blood or other tissues**.** The test detects the mutation in the gene which encodes the prion protein. The presence of a mutation indicates a hereditary form of CJD, FFI, or GSS.

Treatment:

There is currently no proven treatment for TSEs. There are a number of potential treatments in development, however, no treatment to date has been shown to slow or halt the disease.

Case fatality:

The case-fatality rate for any of the TSEs is 100%. Death due to sCJD usually occurs within 3-12 months (the mean is 7 months). vCJD has a longer clinical course of illness than sCJD (a mean of 14 months). Death due to FI, kuru, and GSS usually occur within 1 year, 3-12 months, and 2-6 years, respectively.

Reservoir:

Humans are the only known reservoir for CJD, kuru, GSS, and FI. The reservoir for vCJD is believed to be BSE infected cattle.

Transmission:

The mode of transmission of sCJD and sFI is unknown. It is theorized that sporadic mutations in the normal protein result in disease. fCJD, FFI, and GSS are caused by genetic mutations in the prion protein gene, which causes a change in the amino acid sequence of the normal prion protein. iCJD is acquired following certain medical procedures, such as transplantation of prion-infected corneas or other tissues, the administration of hormones derived from human glands, or by contaminated neurosurgical instruments. Although not firmly established, it is believed that vCJD in humans results from the consumption of contaminated meat or meat by-products from BSE-infected cattle. Person-to-person transmission of kuru occurred through ritual practices involving cannibalism and no longer occurs in persons born after such practices were abandoned.

Susceptibility:

Published and unpublished information indicate that infectivity is found most often and in highest concentration in the central nervous system, specifically the brain, spinal cord and eye. Persons with contact with these organs in cases with TSEs are at greatest risk for acquiring the disease. Familial TSEs (GSS, FFI, fCJD) are caused by genetic mutations in the prion protein gene. The only persons that can acquire these forms are those that are genetically predisposed.

Incubation period:

The incubation period for iatrogenic CJD varies by route of exposure (15 months–30 years). The incubation period is unknown for sCJD and is believed to be variable for vCJD, with some cases having incubation periods as short as 5–10 years.

Period of communicability:

CJD is not infectious in the usual sense; there is no evidence of person-to-person transmission by casual contact. The brain and other neurological tissues may be infectious when handled directly throughout symptomatic illness and possibly during the later stages of the incubation period.

Epidemiology:

Kuru was first identified in the 1950s in Papua, New Guinea among persons who participated in ritual mourning ceremonies involving cannibalism. It was determined that the chain of infection started early in the 20th century, possibly with ingestion of tissue from a person with sCJD. The incidence of kuru declined following cessation of the ceremonies.

Sporadic CJD (sCJD) has been reported worldwide. The annual incidence rate for sCJD is approximately 1 case/1,000,000 population. The highest age-specific incidence rate (over 5 cases/1,000,000 population) occurs in those aged 65–79 years. CJD has been reported in persons aged 14–90 years, with over 95% of cases aged 35 years or older and with the peak of disease onset occurring in the 60–90 year-old age group. Familial CJD has an average age of onset that is approximately ten years younger than sCJD.

In 1996, a new form of CJD, denoted variant CJD (vCJD), was identified in the United Kingdom. The source of vCJD is thought to be cattle with BSE, on the basis of temporal association and some biochemical markers. Over 150 cases of vCJD have been reported worldwide, mainly from the United Kingdom. Variant CJD (vCJD) typically occurs at a younger age than CJD, with disease onset peaking in the 25–29 year-old age group and with a mean age at death of 28 years
(range 12–74 years).

CJD is found everywhere in the world, but it is very rare. Only one in a million people each year will get this disease. Since 1980, 35 Utahans have died of CJD. This number is not higher than normal.

✓PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:

- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention

Prevention:

- Tissue from an infected person can not be used in transplants.
- EEG electrodes and surgical instruments contaminated by tissue infected persons should be appropriately sterilized.
- Meat from cattle herds infected with the agent causing BSE should not be consumed.
- Blood donation should not be accepted from persons at high risk for CJD.
    - History of residence or travel to the UK for three months or longer during 1980-1996, or
    - Persons traveling to other European countries for an extended period of time since 1980.

When determining risk, infectivity of a tissue must be considered together with the route of exposure.

- **Cutaneous exposures** of intact skin or mucous membranes (except those of the eye) poses **negligible risk**; however, it is prudent and highly recommended to avoid such exposure when working with any high infectivity tissue.
- **Transcutaneous exposures**, including contact exposures to non-intact skin or mucous membranes, splashes to the eye, and inoculations via needle or scalpel and other surgical instruments pose a greater **potential risk**. Thus, it is prudent to avoid these types of exposures when working with either low infectivity or high infectivity tissues.
- **Central nervous system (CNS) exposures** (i.e. inoculation of the eye or CNS) with any infectious material poses a very **serious risk**, and appropriate precautions must always be taken to avoid these kinds of exposures.

Chemoprophylaxis:
None.

Vaccine:
None.

Isolation and quarantine requirements:
Isolation: None
Hospital: None
Quarantine: None

✓CASE INVESTIGATION

Reporting:
All persons diagnosed with transmissible spongiform encephalopathies should be reported to public health.

Case definition:
There are currently no case definitions for TSEs. The following case classifications have been determined by WHO.

Sporadic CJD (2003)
Case classification
Possible (Suspect):
- Progressive dementia AND
- EEG atypical or not known AND
- Duration <2 years AND
- At least 2 of the following clinical features:
  - Myoclonus
  - Visual or cerebellar disturbance
  - Pyramidal/extrapyramidal dysfunction
  - Akinetic mutism

Probable: (in the absence of an alternative diagnosis from routine investigation)
- Progressive dementia AND
- A typical EEG, whatever the clinical duration of the disease, AND/OR a positive 14-3-3 assay for CSF and a clinical duration to death <2 years AND
- At least 2 of the following clinical features:
  - Myoclonus
  - Visual or cerebellar disturbance
  - Pyramidal/extrapyramidal dysfunction
  - Akinetic mutism

Definite (*Confirmed)*:
- Neuropathological confirmation AND/OR

- Confirmation of protease-resistant prion protein (immunocytochemistry or western blot) AND/OR
- Presence of scrapie-associated fibrils

Iatrogenically transmitted CJD (2003)

Case classification

Probable:

- Progressive cerebellar syndrome in human pituitary hormone recipients OR
- Probable CJD with recognized iatrogenic risk

Definite (*Confirmed)*:

- Definite CJD with a recognized iatrogenic risk

Genetic human TSEs (GSS and FFI) (2003)

Case classification

Probable:

- Probable TSE plus definite or probable TSE in a first-degree relative OR
- Progressive neuropsychiatric disorder plus disease-specific mutation.

Definite (*Confirmed)*:

- Definite TSE with a recognized pathogenic PrP mutation plus definite or probable TSE in a first degree relative

Variant CJD (2003)

Case classification

Possible (Suspect):

- Progressive neuropsychiatric disorder AND
- Duration of illness > 6 months AND
- Routine investigations do not suggest an alternative diagnosis AND
- No history of potential iatrogenic exposure AND
- No evidence of a familial form of TSE AND
- EEG does not show the typical appearance of sporadic CJD (or no EEG performed) AND
- At least 4 of the following clinical features:
  - Early psychiatric symptoms
  - Persistent painful sensory symptoms
  - Ataxia
  - Myoclonus or chorea or dystonia
  - Dementia

Probable:

- Progressive neuropsychiatric disorder AND
- Duration of illness > 6 months AND
- Routine investigations do not suggest an alternative diagnosis AND
- No history of potential iatrogenic exposure AND

- No evidence of a familial form of TSE AND
- EEG does not show the typical appearance of sporadic CJD (or no EEG performed) AND MRI brain scan shows bilateral symmetrical pulvinar high signal OR ositive tonsil biopsy
- At least 4 of the following clinical features:
  - Early psychiatric symptoms
  - Persistent painful sensory symptoms
  - Ataxia
  - Myoclonus or chorea or dystonia
  - Dementia

Definite (*Confirmed)*:

- Progressive neuropsychiatric disorder AND
- Neuropathological confirmation (spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum) of vCJD

Case Investigation Process:

- Local and state health departments should be notified.
- Appropriate laboratory samples and preliminary clinical and epidemiologic information should be obtained.

Outbreaks:

TSEs do not cause outbreaks in the usual sense. However, if the reported incidence of disease is higher than normal, investigation will be necessary to determine if a common source is causing infection.

Identification of case contacts and management:

Prevention of Iatrogenic CJD

Prion proteins cannot be inactivated by routine methods of decontamination. For any suspect cases of CJD for which a biopsy was performed, confirm with the infection control personnel that appropriate disinfection and sterilization methods were used on the neurosurgical instruments or devices as recommended by the Centers for Disease Control and Prevention (CDC).

✓REFERENCES

Control of Communicable Diseases Manual (18th Edition), Heymann, D.L., Ed; 2004.

Red Book: 2003 Report of the Committee on Infectious Diseases (26th Edition), Larry K. Pickering MD, Ed; 2003.

Principles and Practice of Infectious Disease (6th Edition), Gerald L. Mandell, John E. Bennett, and Raphael Dolin Eds; 2005.

Massachusetts Department of Public Health, Guide to Surveillance, Reporting and Control, 2006.

National Prion Disease Pathology Surveillance Center, Case Western University. http://www.cjdsurveillance.com/. Accessed: July 3, 2007.

WHO Manual for the Surveillance of Human Transmissible Spongiform Encephalopathies, World Health Organization, Communicable Disease Surveillance and Response; 2003. http://www.who.int/bloodproducts/TSE-manual2003.pdf.

WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies, Report of a WHO Consultation; Geneva, Switzerland, 23 –26 March 1999. http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.3.pdf